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| <b>(51) International Patent Classification <sup>6</sup>:</b><br><b>C07D 333/38, A61K 31/415, 31/495, 31/435, C07D 409/12, 409/14, 417/14, 333/70, 409/06, 473/06, 473/34</b>   | <b>A1</b>  | <b>(11) International Publication Number:</b> <b>WO 99/32477</b><br><b>(43) International Publication Date:</b> 1 July 1999 (01.07.99) |
| <b>(21) International Application Number:</b> PCT/EP98/07650<br><b>(22) International Filing Date:</b> 27 November 1998 (27.11.98)<br><br><b>(30) Priority Data:</b><br>08/994,284      19 December 1997 (19.12.97)    US<br>09/187,459      5 November 1998 (05.11.98)      US<br><br><b>(71) Applicant:</b> SCHERING AKTIENGESELLSCHAFT [DE/DE];<br>Müllerstrasse 178, D-13353 Berlin (DE). | <b>(72) Inventors:</b> ARNAIZ, Damian, O.; 103 Bedford, Hercules, CA 94547 (US). CHOU, Yuo-Ling; 1068 Miller Drive, Lafayette, CA 94549 (US). KARANJAWALA, Rushad, E.; 172 Bonaire Avenue, Hercules, CA 94547 (US). KOCHANNY, Monica, J.; 193 Irwin Street, San Rafael, CA 94901 (US). LEE, Wheeseong; 933 Hough Avenue #10, Lafayette, CA 94549 (US). LIANG, Amy, Mei; 5572 Cerro Norte, Richmond, CA 94803 (US). MORRISSEY, Michael, M.; 129 Alta Vista, Danville, CA 94506 (US). PHILLIPS, Gary, B.; 3043 Shetland Drive, Pleasant Hill, CA 94523 (US). SACCHI, Karna, Lyn; 202 Clipper Street #1, San Francisco, CA 94114 (US). SAKATA, Stephen, T.; 1411 Palo Verde Road, Irvine, CA 92612 (US). SHAW, Kenneth, J.; 16 Oakmont Court, San Rafael, CA 94901 (US). SNIDER, R., Michael; 1031 Lorraine Drive, Napa, CA 94558 (US). WU, Shung, C.; 7121 Foxtail Court, Lawrenceville, NJ 08648 (US). YE, Bin; Apartment 3022, 3400 Richmond Parkway, Richmond, CA 94806 (US). ZHAO, Zuchun; 5368 Cerro Sur, El Sobrante, CA 94803 (US). GRIEDEL, Brian, D.; 526 Liberty Street, El Cerrito, CA 94530 (US).<br><br><b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.</i><br><i>With amended claims.</i><br><br><b>Date of publication of the amended claims:</b><br>10 September 1999 (10.09.99) |  |
| <b>(54) Title:</b> ORTHO-ANTHRANILAMIDE DERIVATIVES AS ANTI-COAGULANTS  |  |  |
| <b>(57) Abstract</b><br><p>This invention is directed to compounds of formula (III) wherein B, C, D, E, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are disclosed herein. These compounds are disclosed as being useful as anti-coagulants.</p> <div style="text-align: center;"> <p style="text-align: right;">( III )</p> </div>   |  |  |

## AMENDED CLAIMS

[received by the International Bureau on 26 July 1999 (26.07.99);  
Original claims 68 and 69 amended; remaining claims unchanged (8 pages)]

-C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> or -C(O)N(R<sup>5</sup>)R<sup>6</sup>, or heterocyclalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> and -C(O)N(R<sup>5</sup>)R<sup>6</sup>); or

both R<sup>16</sup>'s together with the nitrogen to which they are attached (and wherein the R<sup>9</sup> substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -C(O)R<sup>5</sup>, -C(O)-(R<sup>8</sup>-O)<sub>t</sub>R<sup>5</sup> (where t is 1 to 6), and -(R<sup>8</sup>-O)<sub>t</sub>R<sup>5</sup> (where t is 1 to 6);

each R<sup>17</sup> is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, or -R<sup>8</sup>-C(O)-N(R<sup>5</sup>)R<sup>6</sup>;

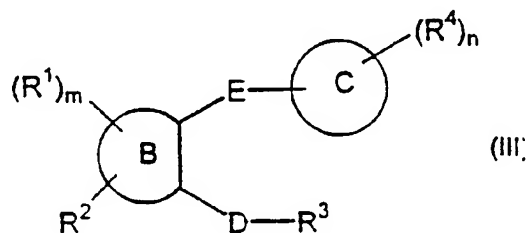
R<sup>18</sup> is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR<sup>5</sup>, or -NO<sub>2</sub>; and

each R<sup>19</sup> is cycloalkyl, haloalkyl, -R<sup>8</sup>-OR<sup>5</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, -R<sup>8</sup>-C(O)N(R<sup>5</sup>)R<sup>6</sup>,

heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> or -C(O)N(R<sup>5</sup>)R<sup>6</sup>), or heterocyclalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> and -C(O)N(R<sup>5</sup>)R<sup>6</sup>);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

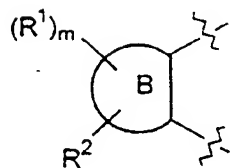
68. Use of a therapeutically effective amount of a compound of formula (III):



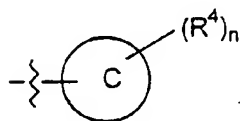
wherein

m is 1 to 3;

n is 1 to 5;



is an aryl or a heterocyclic ring substituted by  $R^2$  and one or more  $R^1$  groups;



is an aryl or a heterocyclic ring substituted by one or more  $R^4$  groups;

D and E are independently a linker selected from the group consisting of  $-N(R^5)-C(X)-$ :

$-R^8-N(R^5)-C(X)-$ ;  $-N(R^5)-C(X)-R^8-$ ;  $-R^8-N(R^5)-C(X)-R^8-$ ;  $-N(R^5)-S(O)_p-$ ;  $-R^8-N(R^5)-S(O)_p-$ ;

$-N(R^5)-S(O)_p-R^8-$ ; and  $-R^8-N(R^5)-S(O)_p-R^8-$  (where p is 0 to 2; X is oxygen, sulfur or  $H_2$ )

where D and E can be attached to the B ring having the  $R^1$  and  $R^2$  substituents by either terminus of the linker;

each  $R^1$  is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano,  $-OR^5$ ,  $-S(O)_p-R^9$

(where p is 0 to 2),  $-C(O)OR^5$ ,  $-C(O)N(R^5)R^6$ ,  $-N(R^5)R^6$ ,  $-O-C(O)R^5$ ,

$-N(R^5)-CH(R^{12})-C(O)OR^5$ , heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  $-OR^5$ ,  $-C(O)OR^5$ ,  $-N(R^5)R^6$  or  $-C(O)N(R^5)R^6$ ) or heterocyclylalkyl (optionally

substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  $-OR^5$ ,  $-C(O)OR^5$ ,  $-N(R^5)R^6$  or

$-C(O)N(R^5)R^6$ ;

$R^2$  is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano,  $-OR^5$ ,  $-S(O)_p-R^9$  (where p is 0 to 2),

$-C(O)OR^5$ ,  $-C(O)N(R^5)R^6$ ,  $-N(R^{10})R^{11}$ ,  $-C(R^7)H-N(R^{10})R^{11}$ ,  $-C(R^7)H-R^8-N(R^{10})R^{11}$ ,

$-C(R^7)H-OR^5$ ,  $-C(R^7)H-R^8-OR^5$ ,  $-C(R^7)H-S(O)_p-R^9$  (where p is 0 to 2),  $-C(R^7)H-R^8-S(O)_p-R^9$

(where p is 0 to 2),  $-O-R^8-S(O)_p-R^9$  (where p is 0 to 2),  $-C(R^7)H-N(R^5)R^6$ ,

$-C(R^7)H-R^8-N(R^5)R^6$ ,  $-O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}$ ,  $-O-R^8-N(R^{10})R^{11}$ ,  $-O-R^8-O-C(O)R^5$ ,

$-O-R^8-CH(OH)-CH_2-OR^5$ ,  $-O-(R^8-O)_t-R^5$  (where t is 1 to 6),  $-O-(R^8-O)_t-R^{19}$  (where t is 1 to

6),  $-O-R^8-C(O)R^5$ ,  $-O-R^8-C(O)R^{19}$ ,  $-O-R^8-C(O)OR^5$ ,  $-N(R^5)-R^8-N(R^{10})R^{11}$ ,

$-S(O)_p-R^8-N(R^5)R^6$  (where p is 0 to 2),  $-S(O)_p-R^8-C(O)OR^5$  (where p is 0 to 2), or

$-N(R^5)-CH(R^{12})-C(O)OR^5$ ;

$R^3$  is aryl or heterocyclyl both substituted by one or more  $R^{14}$  substituents independently selected

from the group consisting of hydrogen, alkyl, halo, formyl, acetyl, cyano,  $-R^8-CN$ ,

$-N(R^{10})R^{11}$ ,  $-R^8-N(R^{10})R^{11}$ ,  $-R^8-N^{\oplus}(R^9)(R^{16})_2$ ,  $-C(O)OR^5$ ,  $-R^8-C(O)OR^5$ ,  $-OR^5$ ,  $-R^8-OR^5$ ,

$-C(R^7)H-O-R^{15}$ ,  $-S(O)_p-R^{15}$  (where p is 0 to 2),  $-R^8-S(O)_p-R^{15}$  (where p is 0 to 2),

$-S(O)_p-N(R^5)R^6$  (where p is 0 to 2),  $-C(O)N(R^5)R^6$ ,  $-R^8-C(O)N(R^5)R^6$ ,  $-N(R^5)-(R^8-O)_t-R^5$

(where t is 1 to 6),  $-R^8-N(R^5)-(R^8-O)_t-R^5$  (where t is 1 to 6),  $-R^8-O-(R^8-O)_t-R^5$  (where t is 1

to 6),  $-O-R^8-CH(OH)-CH_2-OR^5$ ,  $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$ .

-C(R<sup>7</sup>)H-N(R<sup>5</sup>)-R<sup>8</sup>-[CH(OH)]<sub>t</sub>-CH<sub>2</sub>-OR<sup>5</sup> (where t is 1 to 6), -C(R<sup>7</sup>)H-N(R<sup>5</sup>)-S(O)<sub>2</sub>-N(R<sup>10</sup>)R<sup>11</sup>,  
 -C(R<sup>7</sup>)H-N(R<sup>10</sup>)-C(NR<sup>17</sup>)-N(R<sup>10</sup>)R<sup>11</sup>, -C(R<sup>7</sup>)H-N(R<sup>10</sup>)-C(NR<sup>17</sup>)-R<sup>10</sup>, -C(NR<sup>17</sup>)-N(R<sup>5</sup>)R<sup>6</sup>,  
 -C(R<sup>7</sup>)H-C(NR<sup>17</sup>)-N(R<sup>5</sup>)R<sup>6</sup>, -C(R<sup>7</sup>)H-O-N(R<sup>5</sup>)R<sup>6</sup>, heterocyclyl (wherein the heterocyclyl  
 radical is not attached to the rest of the molecule through a nitrogen atom and is optionally  
 substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> or  
 -C(O)N(R<sup>5</sup>)R<sup>6</sup>), and heterocyclylalkyl (wherein the heterocyclyl radical is not attached to  
 the alkyl radical through a nitrogen ring and is optionally substituted by one or more  
 substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  
 -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> and -C(O)N(R<sup>5</sup>)R<sup>6</sup>);

each R<sup>4</sup> is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup>,  
 -C(O)N(R<sup>5</sup>)R<sup>6</sup>, or -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>;

each R<sup>5</sup> and R<sup>6</sup> is independently hydrogen, alkyl, aryl or aralkyl;

each R<sup>7</sup> is independently hydrogen or alkyl;

each R<sup>8</sup> is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R<sup>9</sup> is independently alkyl, aryl or aralkyl;

each R<sup>10</sup> and R<sup>11</sup> is independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, -R<sup>8</sup>-CN,  
 -OR<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -S(O)<sub>p</sub>-R<sup>15</sup> (where p is 0 to 2), -R<sup>8</sup>-S(O)<sub>p</sub>-R<sup>15</sup> (where p is 0 to 2), -N(R<sup>5</sup>)R<sup>6</sup>,  
 -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, -C(O)-R<sup>15</sup>, -C(O)NH<sub>2</sub>, -R<sup>8</sup>-C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -C(O)-S-R<sup>5</sup>,  
 -C(O)-N(R<sup>5</sup>)R<sup>15</sup>, -R<sup>8</sup>-C(O)-N(R<sup>5</sup>)R<sup>15</sup>, -C(S)-N(R<sup>5</sup>)R<sup>15</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)-C(O)H, -R<sup>8</sup>-N(R<sup>5</sup>)-C(O)R<sup>15</sup>,  
 -C(O)O-R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -C(N(R<sup>5</sup>)R<sup>6</sup>)=C(R<sup>18</sup>)R<sup>10</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)-P(O)(OR<sup>5</sup>)<sub>2</sub>, cycloalkyl (optionally  
 substituted by one or more substituents selected from the group consisting of alkyl, halo  
 and -OR<sup>5</sup>), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  
 -OR<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -R<sup>8</sup>-S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2),  
 -N(R<sup>5</sup>)R<sup>6</sup> or -C(O)N(R<sup>5</sup>)R<sup>6</sup>), or heterocyclylalkyl (optionally substituted by one or more  
 substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  
 -OR<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -R<sup>8</sup>-S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2),  
 -N(R<sup>5</sup>)R<sup>6</sup> and -C(O)N(R<sup>5</sup>)R<sup>6</sup>);

or R<sup>10</sup> and R<sup>11</sup> together with the nitrogen to which they are attached form a *N*-heterocyclic ring  
 containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally  
 substituted by one or more substituents selected from the group consisting of alkyl, halo,  
 haloalkyl, aryl, aralkyl, oxo, nitro, cyano, -R<sup>8</sup>-CN, =N(R<sup>17</sup>), -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>,  
 -N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -C(O)N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-C(O)N(R<sup>5</sup>)R<sup>6</sup>, -N(R<sup>5</sup>)-N(R<sup>5</sup>)R<sup>6</sup>, -C(O)R<sup>5</sup>,  
 -C(O)-(R<sup>8</sup>-O)<sub>t</sub>-R<sup>5</sup> (where t is 1 to 6), -S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -R<sup>8</sup>-S(O)<sub>p</sub>-R<sup>9</sup> (where p is  
 0 to 2), -(R<sup>8</sup>-O)<sub>t</sub>-R<sup>5</sup> (where t is 1 to 6), and heterocyclyl (optionally substituted by one or  
 more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl,

$-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$ , and  $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ ;

$\text{R}^{12}$  is a side chain of an  $\alpha$ -amino acid;

each  $\text{R}^{15}$  is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl,  $-\text{R}^8-\text{O}-\text{C}(\text{O})-\text{R}^5$ ,  $-\text{R}^8-\text{OR}^5$ ,

$-\text{N}(\text{R}^5)\text{R}^6$ ,  $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$ ,  $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$ , heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl,  $-\text{OR}^5$ ,  $-\text{R}^8-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$ , and  $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ ), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl,  $-\text{OR}^5$ ,  $-\text{R}^8-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$ , and  $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ );

or  $\text{R}^5$  and  $\text{R}^{15}$  together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino,  $\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ , aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each  $\text{R}^{16}$  is independently alkyl, aryl, aralkyl,  $-\text{R}^8-\text{OR}^5$ ,  $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$ , cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and  $-\text{OR}^5$ ), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl,  $-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$  or  $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ ), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl,  $-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$  and  $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ ); or

both  $\text{R}^{16}$ 's together with the nitrogen to which they are attached (and wherein the  $\text{R}^9$  substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl,  $-\text{OR}^5$ ,  $-\text{R}^8-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$ ,  $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{C}(\text{O})-(\text{R}^8-\text{O})_t-\text{R}^5$  (where  $t$  is 1 to 6), and  $-(\text{R}^8-\text{O})_t-\text{R}^5$  (where  $t$  is 1 to 6);

each  $\text{R}^{17}$  is independently hydrogen, alkyl, aryl, aralkyl, cyano,  $-\text{OR}^5$ ,  $-\text{R}^8-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{C}(\text{O})-\text{N}(\text{R}^5)\text{R}^6$ , or  $-\text{R}^8-\text{C}(\text{O})-\text{N}(\text{R}^5)\text{R}^6$ ;

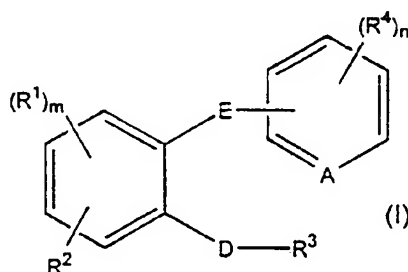
$\text{R}^{18}$  is hydrogen, alkyl, aryl, aralkyl, cyano,  $-\text{C}(\text{O})\text{OR}^5$ , or  $-\text{NO}_2$ ; and

each  $\text{R}^{19}$  is cycloalkyl, haloalkyl,  $-\text{R}^8-\text{OR}^5$ ,  $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$ ,  $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{R}^8-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ , heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl,  $-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$  or  $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ ), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl,  $-\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{N}(\text{R}^5)\text{R}^6$  and  $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$ );

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof;

for the production of a medicament for the treatment of a human having a disease-state characterized by thrombotic activity.

69. Use of Claim 68, of a therapeutically effective amount of a compound of formula (I):



A is =CH- or =N-;

m is 1 to 3;

n is 1 to 4;

D is -N(R<sup>5</sup>)-C(Z)- or -N(R<sup>5</sup>)-S(O)<sub>p</sub>- (where p is 0 to 2; Z is oxygen, sulfur or H<sub>2</sub>; and the nitrogen atom is directly bonded to the phenyl ring having the R<sup>1</sup> and R<sup>2</sup> substituents);

E is -C(Z)-N(R<sup>5</sup>)- or -S(O)<sub>p</sub>-N(R<sup>5</sup>)- (where p is 0 to 2; Z is oxygen, sulfur or H<sub>2</sub>; and the nitrogen atom can be bonded to the phenyl ring having the R<sup>1</sup> and the R<sup>2</sup> substituents or to the aromatic ring having the R<sup>4</sup> substituent);

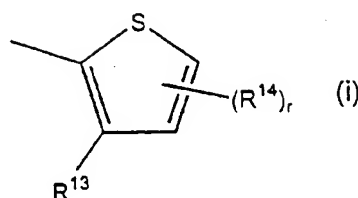
each R<sup>1</sup> is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR<sup>5</sup>, -S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -C(O)OR<sup>5</sup>, -C(O)N(R<sup>5</sup>)R<sup>6</sup>, -N(R<sup>5</sup>)R<sup>6</sup>, -O-C(O)R<sup>5</sup>, or -N(R<sup>5</sup>)-CH(R<sup>12</sup>)-C(O)OR<sup>5</sup>;

or two adjacent R<sup>1</sup>'s together with the carbons to which they are attached form a heterocyclic ring fused to the phenyl ring wherein the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl and aralkyl;

R<sup>2</sup> is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR<sup>5</sup>, -S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -C(O)OR<sup>5</sup>, -C(O)N(R<sup>5</sup>)R<sup>6</sup>, -N(R<sup>10</sup>)R<sup>11</sup>, -C(R<sup>7</sup>)H-N(R<sup>10</sup>)R<sup>11</sup>, -C(R<sup>7</sup>)H-R<sup>8</sup>-N(R<sup>10</sup>)R<sup>11</sup>, -C(R<sup>7</sup>)H-OR<sup>5</sup>, -C(R<sup>7</sup>)H-R<sup>8</sup>-OR<sup>5</sup>, -C(R<sup>7</sup>)H-S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -C(R<sup>7</sup>)H-R<sup>8</sup>-S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -O-R<sup>8</sup>-S(O)<sub>p</sub>-R<sup>9</sup> (where p is 0 to 2), -C(R<sup>7</sup>)H-N(R<sup>5</sup>)R<sup>6</sup>, -C(R<sup>7</sup>)H-R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -O-R<sup>8</sup>-CH(OH)-CH<sub>2</sub>-N(R<sup>10</sup>)R<sup>11</sup>, -O-R<sup>8</sup>-N(R<sup>10</sup>)R<sup>11</sup>, -O-R<sup>8</sup>-O-C(O)R<sup>5</sup>, -O-R<sup>8</sup>-CH(OH)-CH<sub>2</sub>-OR<sup>5</sup>, -O-(R<sup>8</sup>-O)<sub>t</sub>-R<sup>5</sup> (where t is 1 to 6), -O-(R<sup>8</sup>-O)<sub>t</sub>-R<sup>19</sup> (where t is 1 to 6), -O-R<sup>8</sup>-C(O)R<sup>5</sup>, -O-R<sup>8</sup>-C(O)R<sup>19</sup>, -O-R<sup>8</sup>-C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)-R<sup>8</sup>-N(R<sup>10</sup>)R<sup>11</sup>, -S(O)<sub>p</sub>-R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup> (where p is 0 to 2), -S(O)<sub>p</sub>-R<sup>8</sup>-C(O)OR<sup>5</sup> (where p is 0 to 2), or -N(R<sup>5</sup>)-CH(R<sup>12</sup>)-C(O)OR<sup>5</sup>;

R<sup>3</sup> is a radical of formula (I):

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where:

$r$  is 1 or 2;

$R^{13}$  is hydrogen, alkyl, halo, haloalkyl,  $-N(R^5)R^6$ ,  $-C(R^7)H-N(R^5)R^6$ ,  $-OR^5$ ,  $-R^8-OR^5$ ,

$-S(O)_p-R^8-N(R^5)R^6$  (where  $p$  is 0 to 2) or heterocyclalkyl (where the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, aralkyl, nitro and cyano); and

each  $R^{14}$  is independently hydrogen, alkyl, halo, formyl, acetyl, cyano,  $-R^8-CN$ ,  $-N(R^{10})R^{11}$ ,

$-C(R^7)H-N(R^{10})R^{11}$ ,  $-C(R^7)H-R^8-N(R^{10})R^{11}$ ,  $-C(R^7)H-N^+(R^9)(R^{16})_2$ ,

$-C(R^7)H-R^8-N^+(R^9)(R^{16})_2$ ,  $-C(O)OR^5$ ,  $-C(R^7)H-C(O)OR^5$ ,  $-C(R^7)H-R^8-C(O)OR^5$ ,

$-OR^5$ ,  $-C(R^7)H-OR^5$ ,  $-C(R^7)H-R^8-OR^5$ ,  $-C(R^7)H-O-R^{15}$ ,  $-S(O)_p-R^{15}$  (where  $p$  is 0 to

2),  $-C(R^7)H-S(O)_p-R^{15}$  (where  $p$  is 0 to 2),  $-C(R^7)H-R^8-S(O)_p-R^{15}$  (where  $p$  is 0 to 2),

$-S(O)_p-N(R^5)R^6$  (where  $p$  is 0 to 2),  $-C(O)N(R^5)R^6$ ,  $-C(R^7)H-C(O)N(R^5)R^6$ ,

$-C(R^7)H-R^8-C(O)N(R^5)R^6$ ,  $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$  (where  $t$  is 1 to 6),

$-C(R^7)H-R^8-N(R^5)-(R^8-O)_t-R^5$  (where  $t$  is 1 to 6),  $-C(R^7)H-O-(R^8-O)_t-R^5$  (where  $t$  is 1

to 6),  $-C(R^7)H-R^8-O-(R^8-O)_t-R^5$  (where  $t$  is 1 to 6),  $-O-R^8-CH(OH)-CH_2-OR^5$ ,

$-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$ ,  $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$  (where  $t$  is

1 to 6),  $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$ ,  $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$ ,

$-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$ ,  $-C(NR^{17})-N(R^5)R^6$ ,  $-C(R^7)H-C(NR^{17})-N(R^5)R^6$ ,

$-C(R^7)H-O-N(R^5)R^6$ , heterocyclyl (wherein the heterocyclyl radical is not attached

to the radical of formula (i) through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  $-OR^5$ ,  $-C(O)OR^5$ ,  $-N(R^5)R^6$  or

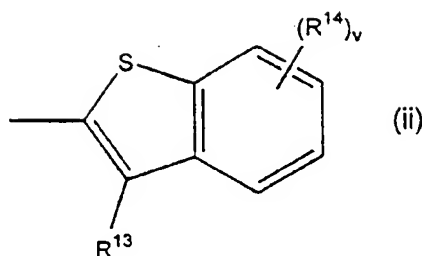
$-C(O)N(R^5)R^6$ ), or heterocyclalkyl (wherein the heterocyclalkyl radical is not

attached to the alkyl radical through a nitrogen atom and is optionally substituted

by one or more substituents selected from the group consisting of alkyl, aryl,

aralkyl, halo, haloalkyl, oxo,  $-OR^5$ ,  $-C(O)OR^5$ ,  $-N(R^5)R^6$  and  $-C(O)N(R^5)R^6$ ;

or  $R^3$  is a radical of the formula (ii):



where  $v$  is 1 to 4;

$R^{13}$  is as defined above for formula (i); and

$R^{14}$  is as defined above for formula (i);

each  $R^4$  is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro,  $-OR^5$ ,  $-C(O)OR^5$ ,  $-N(R^5)R^6$ ,  $-C(O)N(R^5)R^6$ , or  $-R^8-N(R^5)R^6$ ;

$R^5$  and  $R^6$  are each independently hydrogen, alkyl, aryl or aralkyl;

each  $R^7$  is independently hydrogen or alkyl;

each  $R^8$  is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each  $R^9$  is independently alkyl, aryl or aralkyl;

$R^{10}$  and  $R^{11}$  are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano,  $-R^8-CN$ ,  $-OR^5$ ,  $-R^8-OR^5$ ,  $-S(O)_p-R^{15}$  (where  $p$  is 0 to 2),  $-R^8-S(O)_p-R^{15}$  (where  $p$  is 0 to 2),  $-N(R^5)R^6$ ,  $-R^8-N(R^5)R^6$ ,  $-R^8-C(O)OR^5$ ,  $-C(O)-R^{15}$ ,  $-C(O)NH_2$ ,  $-R^8-C(O)NH_2$ ,  $-C(S)NH_2$ ,  $-C(O)-S-R^5$ ,  $-C(O)-N(R^5)R^{15}$ ,  $-R^8-C(O)-N(R^5)R^{15}$ ,  $-C(S)-N(R^5)R^{15}$ ,  $-R^8-N(R^5)-C(O)H$ ,  $-R^8-N(R^5)-C(O)R^{15}$ ,  $-C(O)O-R^8-N(R^5)R^6$ ,  $-C(N(R^5)R^6)=C(R^{18})R^{10}$ ,  $-R^8-N(R^5)-P(O)(OR^5)_2$ , cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and  $-OR^5$ ), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  $-OR^5$ ,  $-R^8-OR^5$ ,  $-C(O)OR^5$ ,  $-S(O)_p-R^9$  (where  $p$  is 0 to 2),  $-R^8-S(O)_p-R^9$  (where  $p$  is 0 to 2),  $-N(R^5)R^6$  or  $-C(O)N(R^5)R^6$ ), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo,  $-OR^5$ ,  $-R^8-OR^5$ ,  $-C(O)OR^5$ ,  $-S(O)_p-R^9$  (where  $p$  is 0 to 2),  $-R^8-S(O)_p-R^9$  (where  $p$  is 0 to 2),  $-N(R^5)R^6$  and  $-C(O)N(R^5)R^6$ );

or  $R^{10}$  and  $R^{11}$  together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano,  $-R^8-CN$ ,  $=N(R^{17})$ ,  $-OR^5$ ,  $-C(O)OR^5$ ,  $-R^8-C(O)OR^5$ ,  $-N(R^5)R^6$ ,  $-R^8-N(R^5)R^6$ ,  $-C(O)N(R^5)R^6$ ,  $-R^8-C(O)N(R^5)R^6$ ,  $-N(R^5)-N(R^5)R^6$ ,  $-C(O)R^5$ ,  $-C(O)-(R^8-O)_t-R^5$  (where  $t$  is 1 to 6),  $-S(O)_p-R^9$  (where  $p$  is 0 to 2),  $-R^8-S(O)_p-R^9$  (where  $p$  is 0 to 2),  $-(R^8-O)_t-R^5$  (where  $t$  is 1 to 6), and heterocyclyl (optionally substituted by one or



more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup>, and -C(O)N(R<sup>5</sup>)R<sup>6</sup>;

R<sup>12</sup> is a side chain of an  $\alpha$ -amino acid;

each R<sup>15</sup> is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, -R<sup>8</sup>-O-C(O)-R<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup>, and -C(O)N(R<sup>5</sup>)R<sup>6</sup>), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup>, and -C(O)N(R<sup>5</sup>)R<sup>6</sup>);

or R<sup>5</sup> and R<sup>15</sup> together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R<sup>16</sup> is independently alkyl, aryl, aralkyl, -R<sup>8</sup>-OR<sup>5</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR<sup>5</sup>), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> or -C(O)N(R<sup>5</sup>)R<sup>6</sup>), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> and -C(O)N(R<sup>5</sup>)R<sup>6</sup>); or

both R<sup>16</sup>'s together with the nitrogen to which they are attached (and wherein the R<sup>9</sup> substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -C(O)R<sup>5</sup>, -C(O)-(R<sup>8</sup>-O)<sub>t</sub>-R<sup>5</sup> (where *t* is 1 to 6), and -(R<sup>8</sup>-O)<sub>t</sub>-R<sup>5</sup> (where *t* is 1 to 6);

each R<sup>17</sup> is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR<sup>5</sup>, -R<sup>8</sup>-OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, -C(O)-N(R<sup>5</sup>)R<sup>6</sup>, or -R<sup>8</sup>-C(O)-N(R<sup>5</sup>)R<sup>6</sup>;

R<sup>18</sup> is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR<sup>5</sup>, or -NO<sub>2</sub>; and

each R<sup>19</sup> is cycloalkyl, haloalkyl, -R<sup>8</sup>-OR<sup>5</sup>, -R<sup>8</sup>-N(R<sup>5</sup>)R<sup>6</sup>, -R<sup>8</sup>-C(O)OR<sup>5</sup>, -R<sup>8</sup>-C(O)N(R<sup>5</sup>)R<sup>6</sup>, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> or -C(O)N(R<sup>5</sup>)R<sup>6</sup>), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR<sup>5</sup>, -C(O)OR<sup>5</sup>, -N(R<sup>5</sup>)R<sup>6</sup> and -C(O)N(R<sup>5</sup>)R<sup>6</sup>);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, for the production of a medicament for the treatment of a human having a disease-state characterized by thrombotic activity.